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ELECTROPHYSIOLOGIC AND ANTIARRHYTHMIC EFFECTS OF INTRAVENOUS BISOPROLOL IN ATRIOVENTRICULAR NODAL REENTRY TACHYCARDIA

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ABSTRACT

Beta-blockade may be useful in the termination and prevention of atrioventricular nodal reentry tachycardia (AVNRT). An electrophysiologic study was performed in 9 patients (4 men and 5 women; mean \pm SD age, 56 ± 16 years) with documented AVNRT before and after the intravenous administration of 5 mg of bisoprolol. In 5 of the 9 patients, AVNRT was terminated by bisoprolol, and AVNRT could no longer be induced in 6 of the 9 patients. Bisoprolol significantly prolonged the Wenckebach cycle length but did not affect fast pathway refractoriness or atrioventricular (AV) nodal conduction time during sinus rhythm or various paced cycle lengths up to 430 milliseconds. Conversely, it significantly prolonged the mean atrium-His bundle (AH) interval during AVNRT from 244 ± 65 milliseconds to 320 ± 64 milliseconds. These observations suggest that the effects of bisoprolol on the AV node, primarily at short cycle lengths, are rate dependent. Due to AH prolongation, mean tachycardia cycle length significantly increased from 313 ± 58 milliseconds to 378 ± 50 milliseconds, but there was no difference in the relative amount of prolongation between responders (60.8 ± 26 ms) and nonresponders (64.6 ± 37 ms). Bisoprolol appears to be useful in the termination and prevention of AVNRT during programmed electrical stimulation studies. Its effects on the AV node are use dependent.

INTRODUCTION

The induction and maintenance of atrioventricular nodal reentry tachycardia (AVNRT) are frequently associated with enhanced sympathetic tone.^{1,2} Beta-blockers may decrease atrioventricular (AV) conduction and increase the duration of AV-nodal refractoriness.³ These drugs are effective in preventing reinduction of AVNRT by programmed electrical stimulation (PES) and may suppress clinical attacks.⁴⁻⁶ Bisoprolol is a new, highly beta₁-selective adrenoceptor blocking drug without intrinsic sympathomimetic activity or membrane-stabilizing activity.^{7,8} Bisoprolol has

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not been studied in AVNRT. Because of its pure β_1 -adrenoreceptor blocking properties, bisoprolol may be especially effective in the adrenergic-dependent forms of supraventricular tachycardias.^{9,10}

The objective of the present study was to investigate the acute effects of bisoprolol on AV-nodal function and initiation and termination of tachycardia in patients with AVNRT.

PATIENTS AND METHODS

Patients

Consecutive patients presenting with symptomatic and sustained AVNRT, defined as narrow QRS tachycardia lasting at least 30 seconds, with a diagnosis confirmed by PES, were enrolled in the study. Only patients with symptomatic AVNRT were included; symptoms included dizziness, palpitations, chest pain, and syncope. Excluded were patients with chronic obstructive lung disease and heart failure and patients in whom digitalis and other antiarrhythmic agents, including β -blockers, could not be withdrawn.

The study protocol was approved by the institutional review board of Groningen University Hospital, Groningen, The Netherlands. Patients were included in the study only after having given their written informed consent to participate.

Study Design

To evaluate the characteristics of AVNRT at baseline, a 24-hour ambulatory electrocardiographic monitor and upright bicycle exercise test were performed. In addition, an arrhythmia questionnaire was completed. Bisoprolol was tested during subsequent PES.

PES was performed in patients in a nonsedated state after they fasted overnight. After local lidocaine anesthesia (20 mL of a 1% solution), three catheters (U.S.C.I. Bard Electrophysiology, Billerica, Massachusetts) were introduced via a femoral vein. One 6-French quadripolar catheter was positioned in the high right atrium, and one 6-French quadripolar catheter was positioned in the right ventricular apex. Lastly, a 5-French bipolar catheter was placed across the tricuspid valve in the His bundle region. One additional 6-French quadripolar catheter was introduced via the right internal jugular vein or the left subclavian vein and positioned in the coronary sinus. Blood pressure was continuously monitored through a 5-French arterial catheter in the right femoral artery. Surface electrocardiographic leads I, II, III, and V_1 were displayed on a monitor together with intracardiac electrograms and recorded on a paperchart recorder or on a

computerized system for electrophysiologic signals (EP Lab, Quinton Instruments, Milwaukee, Wisconsin). During the electrophysiologic study, refractoriness of the atrium, the AV conduction system, and the ventricle were determined using the extrastimulus technique during sinus rhythm and basic cycle lengths of 600, 500, or 430 milliseconds, with A₁S₂ (the interval between the last spontaneous atrial beat and the extra stimulus) or S₁S₂ (the interval between the last driven beat and the extra stimulus), decreasing in steps of 10 milliseconds. AVNRT was defined using accepted electrophysiologic criteria.¹¹ The presence of dual AV-nodal pathways was determined using single atrial extra stimuli and was defined as an abrupt prolongation of the atrium–His bundle (AH) interval of at least 50 milliseconds, after decreasing the extrastimulus interval by 10 milliseconds.^{12–14} AVNRT was diagnosed only if intra-AV–nodal reentry was sustained independent of atrial or ventricular activation.¹³ Sinus node recovery time and sinoatrial conduction time were determined using the method of Strauss et al.¹⁵

Ten minutes after the induction of AVNRT, 5 mg of bisoprolol was given intravenously over a period of 5 minutes, according to a schedule used previously.^{9,10} Forty-five minutes after the end of this bolus injection, all electrophysiologic measurements were repeated. If the tachycardia did not terminate within 45 minutes after administration of bisoprolol, it was terminated by means of overpacing with critically timed atrial or ventricular extra stimuli.

Statistical Analysis

All data were analyzed descriptively. For continuous variables, the mean (\pm SD), the median, and distribution parameters were calculated. Electrophysiologic data from baseline were compared with data obtained after bisoprolol infusion. Student's *t* test was used for the statistical analysis of paired data.

RESULTS

Nine patients (4 men and 5 women; age range 44 to 70 years; mean \pm SD age, 56 ± 16 years) with typical AVNRT were included in the study. All patients had documented supraventricular tachycardia on a 12-lead electrocardiogram. Two patients had daily attacks of tachycardia characterized by episodes of palpitations lasting at least 1 minute, accompanied by chest pain. Four patients experienced weekly episodes of palpitations; in two of these patients, the palpitations were accompanied by chest pain, and in three of these patients, the palpitations were accompanied by presyncope. Three patients had monthly episodes of palpitations; in two of these patients, the palpitations were occasionally accompanied by syncope,

whereas the other patient complained of chest pain and dizziness during these attacks.

All patients had been treated unsuccessfully with antiarrhythmic drugs (2 patients had received propranolol, 1 had received sotalol, 1 had received flecainide, 4 had received verapamil, and 1 had received disopyramide combined with verapamil). There were no episodes of tachycardia during bicycle exercise testing.¹⁶ During Holter monitoring, all patients had symptomatic episodes of narrow complex tachycardia. In total, 14 symptomatic episodes of nonsustained supraventricular tachycardias were registered.

The electrophysiologic variables before and after administration of bisoprolol are summarized in the table. Apart from a significant prolongation of the sinus cycle length, the AH interval, and the Wenckebach point ($P < 0.05$), there were no significant changes in electrocardiographic and intracardiac conduction intervals and refractory periods during sinus rhythm or paced cycle lengths. In seven of the nine patients, dual AV-nodal physiology was demonstrated at baseline.

After the initiation of AVNRT, bisoprolol terminated the arrhythmias in five patients. In the other patients, tachycardia was terminated 45 minutes after the start of bisoprolol, with one critically timed extra stimulus in the right ventricular apex in one patient and 2 or 3 critically timed extra stimuli in the right atrium in the three other patients.

Table. Electrocardiographic (ECG) and electrophysiologic variables before and after administration of bisoprolol. Values are given as mean \pm SD.

	Baseline (ms)	Bisoprolol (ms)
Sinus cycle length*	758 \pm 133	813 \pm 107†
AH interval	71 \pm 18	83 \pm 25†
HV interval	44 \pm 6	40 \pm 7
Sinoatrial conduction time	116 \pm 48	145 \pm 59
SNRT		
550 ms‡	945 \pm 89	1038 \pm 154†
500 ms	978 \pm 102	1046 \pm 151†
450 ms	867 \pm 199	1080 \pm 176†
400 ms	851 \pm 179	960 \pm 163†
QRS width	95 \pm 19	94 \pm 14
Wenckebach point	272 \pm 41	338 \pm 57†
QT time	351 \pm 36	333 \pm 52
Refractory period HRA	245 \pm 29	250 \pm 37
Refractory period RVA	255 \pm 18	247 \pm 17
Tachycardia cycle length		
Minimum	313 \pm 58	378 \pm 50†
Maximum	328 \pm 40	408 \pm 61†

ms = milliseconds; AH = atrium-His bundle; HV = His bundle-ventricle; SNRT = sinus node recovery time; QRS = electrocardiographic (ECG) wave segment; HRA = high right atrium; RVA = right ventricular apex.

* Atrial and ventricular refractory periods were determined at basic cycle length of 500 milliseconds.

† $P < 0.05$.

‡ SNRT determined after atrial burst pacing at cycle lengths of 550, 500, 450, and 400 milliseconds.

Mean tachycardia cycle length (TCL) increased from 313 ± 58 milliseconds to 378 ± 50 milliseconds ($P < 0.05$) 10 minutes after the start of bisoprolol and was 380 ± 33 milliseconds 30 minutes later ($P < 0.05$). Patients in whom tachycardia was terminated with bisoprolol had a similar increase in TCL (60.8 ± 26 milliseconds) compared with the other patients (64.6 ± 37 milliseconds). The change in cycle length was due to a significant increase in the AH interval from 244 ± 65 milliseconds to 320 ± 64 milliseconds, 5 minutes after the start of the infusion ($P \leq 0.05$). Forty-five minutes after the end of the infusion, AVNRT could not be reinduced in six patients. Tachycardia was no longer inducible in four of the five patients in whom tachycardia was terminated with bisoprolol. Also, in two other patients, in whom the arrhythmias were terminated with extra stimuli, AVNRT was no longer inducible. The relationship between TCL and the AH and His bundle–atrium intervals during tachycardia is shown in Figure 1.

In all patients, there was a marked drop in blood pressure after initiation of AVNRT. The relationship between TCL and mean systolic blood pressure is shown in Figure 2.

The mean systolic blood pressure decreased from 130 ± 16 mm Hg to

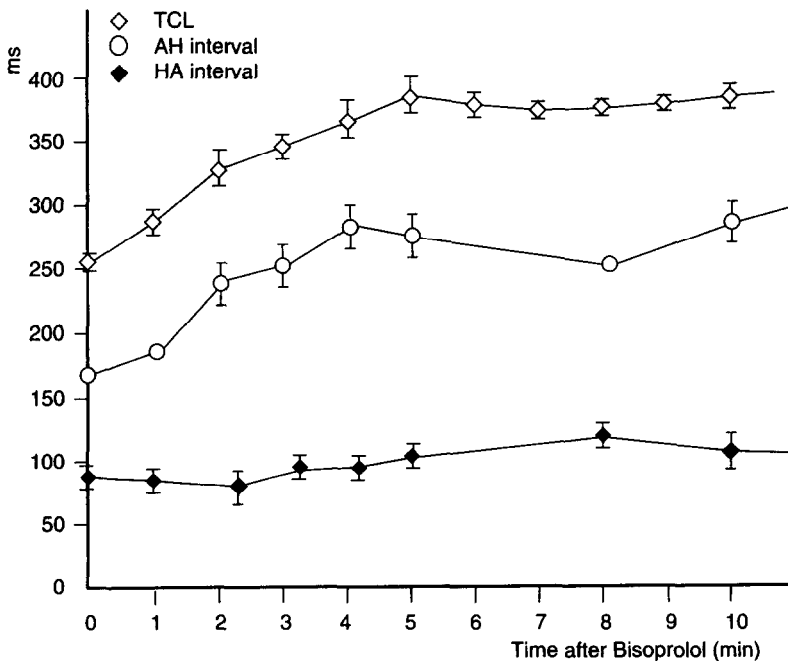


Figure 1. The relationship between tachycardia cycle lengths (TCL), atrium–His bundle (AH) intervals, and His bundle–atrium (HA) intervals. Values are given as mean \pm SE. Note that the increase in TCL is due mainly to the increase in the AH intervals. ms = milliseconds.

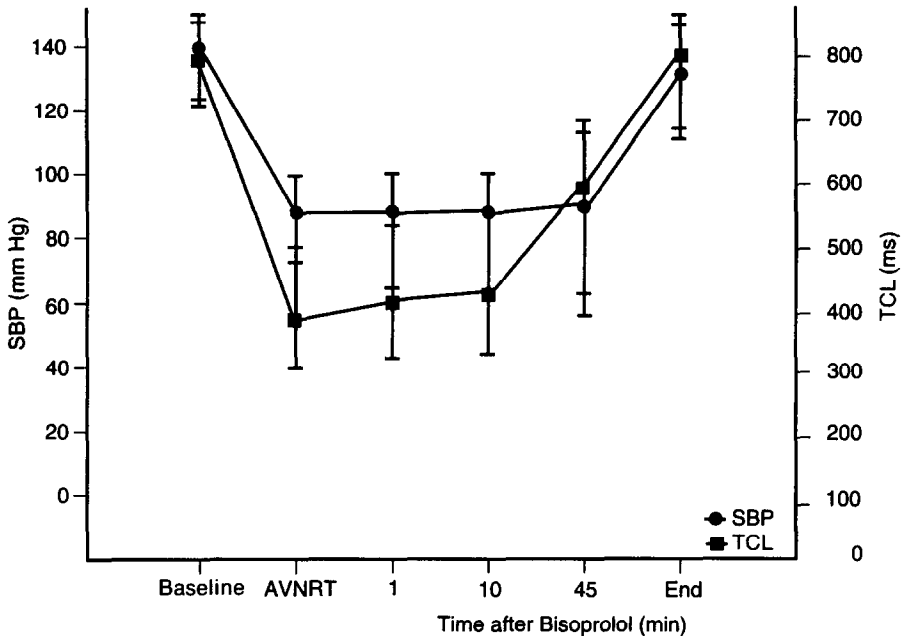


Figure 2. Systolic blood pressure (SBP) and tachycardia cycle length (TCL) in all patients at baseline (during sinus rhythm), immediately after the onset of atrioventricular nodal reentry tachycardia (AVNRT), and 1, 10, and 45 minutes after the start of bisoprolol and at the end of programmed electrical stimulation. Values are given as mean \pm SD. ms = milliseconds.

119 \pm 26 mm Hg. This initial drop in blood pressure was not aggravated by the administration of bisoprolol. Ten minutes after drug administration, mean systolic blood pressure was 118 \pm 16 mm Hg. The increase in TCL due to bisoprolol was paralleled by an increase in blood pressure.

Adverse events observed by the investigator or study nurse or reported by the patient were to be documented on the case record form. However, no adverse events were reported.

DISCUSSION AND CONCLUSIONS

In five of nine patients with induced, sustained AVNRT, tachyarrhythmias were terminated within 45 minutes after the intravenous administration of bisoprolol. After bisoprolol, tachycardia was no longer inducible in six patients. In all patients, termination of the arrhythmias was associated with a significant slowing of the tachycardia due to the slowing of the anterograde slow pathway conduction as evidenced by an increase in the AH interval during AVNRT. Obviously, these results should be interpreted with caution because this was an uncontrolled, open-label study.

AVNRT is often encountered in patients without any further evidence of cardiovascular disease. This may hold true especially for young pa-

tients.¹⁷ AV-nodal tachycardia is mostly due to reentry within the AV node, based on critical differences in conduction time. Presumably, the differences in conduction times are preexistent but may become enhanced by fibrosis or myxedema infiltration of the AV node such as occurs in patients with hypothyroidism. In one of the patients in this study, hypothyroidism may have contributed to AVNRT. In the older patients in this study, fibrosis may have played a role in the development of AVNRT. The oldest patient in this study, a 70-year-old woman, is noteworthy because she only had a brief history of complaints of palpitations and syncope. Apart from these considerations, the effects of catecholamines on the AV node appear to have been an important pathogenic factor in this patient group, which is consistent with the relatively high efficacy of beta-blockage with bisoprolol.²

Adrenergic blockade slows conduction and prolongs refractoriness in both the anterograde and retrograde directions. With regard to the effects of bisoprolol on electrocardiographic and intracardiac conduction times as well as on refractory periods, the data are in agreement with that found with other beta-blockers.¹⁸ The same holds true for the termination of induced AVNRT. In the current study, a high percentage of AVNRT termination (56%) and prevention of reinitiation of AVNRT (67%) was found. Although the use of bisoprolol has been investigated previously in three electrophysiologic studies,^{9,10,19} these investigations did not study AVNRT. The fact that bisoprolol exerts its influence mainly on the AV node is in keeping with its selective beta-adrenergic antagonism. It is well known that intravenous beta-adrenergic blockers given to patients at rest have little or no effect on accessory pathway refractoriness and conduction.^{20,21} The slowing and termination of AVNRT are, however, mainly due to the effect of bisoprolol on slow pathway conduction. In addition, bisoprolol may suppress premature atrial beats, which may initiate AVNRT. Therefore, intravenous beta-blockade may be effective in terminating AVNRT, especially in patients in whom initiation and sustaining of the arrhythmia is dependent on an increased sympathetic drive.

Results from the Cardiac Arrhythmia Suppression Trial and preliminary results from the Survival with Oral D-Sotalol trial have indicated that class Ic and class III drugs may provoke ventricular proarrhythmias.²² Beta-blockade does not provoke this type of proarrhythmia.¹⁸ On the other hand, beta-blockade may aggravate sick sinus syndrome or compromise AV-nodal conduction. However, the latter is unlikely in a relatively young patient population suffering from AVNRT. AVNRT may also be treated with radiofrequency ablation techniques, but the latter are still associated with a significant rate of recurrence of arrhythmias and risk of AV block, necessitating pacemaker implantation.²³

A relatively low dose (5 mg) of bisoprolol given intravenously was chosen to avoid aggravation of the hypotension that can be expected after

induction of tachyarrhythmia.^{3,11} No detrimental effects on hemodynamic performance were found. The rise in blood pressure during the induced tachycardia seen in all patients after intravenous administration of bisoprolol was accompanied by a significant slowing of the tachycardia. Therefore, rate appears to be the most important determinant of blood pressure reduction during AVNRT, and blood pressure is not negatively affected by bisoprolol. This suggests that the increased duration of diastole (with the atrial contribution to filling still absent) played an important part in the increase in blood pressure. Apart from its high β_1 -selectivity, the fact that bisoprolol did not aggravate the hypotension caused by AVNRT is a favorable property of this drug and warrants further investigation with a higher dose and/or comparison with other beta-blockers, especially in patients with adrenergic-drive-dependent AVNRT.⁸ Further research into the efficacy of oral beta-blocker treatment for the prevention of AVNRT appears indicated, especially in view of the adverse effects of class Ic and class III agents and the risks of radiofrequency ablation.²³

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References:

1. Zipes DP. Atrioventricular nodal re-entrant tachycardia. In: Braunwald E, ed. *Heart Disease*. Philadelphia: WB Saunders; 1984:707–710.
2. Hariman RJ, Gomes JA, El Sherif N. Catecholamine dependent atrio-ventricular nodal re-entrant tachycardia. *Circulation*. 1983;67:681–685.
3. Jazayeri MR, Jasbir SS, Akhtar M. Atrioventricular nodal re-entrant tachycardia. Electrophysiologic characteristics, therapeutic interventions and specific reference to anatomic boundary of the re-entrant circuit. *Cardiol Clin*. 1993;11:151–184.
4. Wu D, Denes P, Wyndham C, et al. The effects of propranolol on induction of A-V nodal re-entrant paroxysmal tachycardia. *Circulation*. 1974;50:665–677.
5. Chang MS. Nadolol and supraventricular tachycardia: An electrophysiologic study. *J Am Coll Cardiol*. 1983;2:894–903.
6. Rizos I. Differential effects of sotalol and metoprolol on induction of paroxysmal supraventricular tachycardia. *Am J Cardiol*. 1994;53:1022–1027.
7. Leopold G. Balanced pharmacokinetics and metabolism of bisoprolol. *J Cardiovasc Pharmacol*. 1986;8(Suppl):S16–S20.
8. Haeusler G, Schliep HJ, Schelling P, et al. High beta-1-selectivity and favorable pharmacokinetics as the outstanding properties of bisoprolol. *J Cardiovasc Pharmacol*. 1986;8(Suppl):S2–S15.
9. Proclemer A, Gradnik R, Savinitto S, et al. Electrophysiological effects of bisoprolol. *Eur Heart J*. 1987;8(Suppl M):81–85.

10. Neuss H, Conrad A, Mitrovic V, et al. Electrophysiologic effects of an acute β -blockade induced by bisoprolol in patients with supraventricular tachycardia as assessed by His-bundle electrograms. *J Cardiovasc Pharmacol*. 1986;8(Suppl 11):S167–S170.
11. Josephson ME, Seides FS. Electrophysiologic investigators: General concepts. In: *Clinical Cardiac Electrophysiology, Techniques and Interpretations*. Philadelphia: Lea & Febiger; 1979:147–190.
12. Moe GK, Preston JB, Burlington H. Physiologic evidence for a dual AV-transmission system. *Circ Res*. 1956;4:357–365.
13. Denes P, Wu D, Dhingra K. Atrio-ventricular nodal pathways: A common electrophysiologic response. *Br Heart J*. 1975;37:1069–1075.
14. Akhtar M, Gilbert CJ, Wolf FG. Atrioventricular nodal reentry. *Circulation*. 1979;59:1252–1254.
15. Strauss HC, Saroff AL, Bigger JT, et al. Premature atrial stimulation as a key to understanding of sinoatrial conduction in man. *Circulation*. 1973;47:86–93.
16. Tuininga YS, Crijns HJGM, Wiesfeld ACP, et al. Electrographic patterns relative to initiating mechanisms of exercise-induced ventricular tachycardia. *Am Heart J*. 1993;126:359–367.
17. Pentinga ML, Meeder JG, Crijns HJGM, et al. Late onset atrioventricular nodal tachycardia. *Int J Cardiol*. 1993;38:293–298.
18. Morganroth J. Risk factors for the development of proarrhythmic events. *Am J Cardiol*. 1987;59:32E–37E.
19. Verroste JM, Van Hemel NM, Kingma JH. Interaction of bisoprolol and procainamide in human cardiac impulse generation and conduction. *J Cardiovasc Pharmacol*. 1990;16(Suppl 5):S193–S195.
20. Denes P, Cummings JM, Simpson R. Effects of propranolol on anomalous pathway refractoriness and circus movement tachycardias in patients with preexcitation. *Am J Cardiol*. 1978;41:1061–1067.
21. Coumel P, Escoubet B, Attuel P. Beta-blocking therapy in atrial and ventricular tachyarrhythmias: Experience with nadolol. *Am Heart J*. 1984;108:1098–1108.
22. CAST Investigators Preliminary Report. Effects of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *NEJM*. 1989;321:406–412.
23. Hindricks G, on behalf of the Multicentre European Radiofrequency Survey (MERFS). Complications of radiofrequency catheter ablation of arrhythmias. *Eur Heart J*. 1993;14:1644–1653.